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Editorial

Hepatitis C after simultaneous liver–kidney transplantation ☆

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See Article, pages 874–880

The introduction of the MELD score for organ allocation in liver transplantation led to an increased emphasis on renal impairment and to a proliferation of simultaneous liver–kidney transplantation (SLK). While the discussion on criteria is ongoing, information on the natural history and management of recurrent hepatitis C in this situation is lacking and consists mostly of small retrospective reports based on the experience of single centers.

The study appearing in this issue by Van Wagner et al. [1] reports the outcome of recurrent hepatitis C after SLK in 38 patients at the Northwestern University Transplantation Center. Thirty-eight hepatitis C virus (HCV)-positive patients undergoing liver transplantation alone (LTA) in the same year serve as controls. The design is retrospective, involving all SLK patients transplanted between June 1999 and 2006. The median time of observation after transplant was 34 months in the SLK group and 41 months in the LTA group. Recurrence rates were somewhat higher in LTA patients but there was no significant difference with respect to long-term patient and graft survival, time to hepatitis C recurrence, percent >stage 2 fibrosis, renal function and graft function between the two groups. Treatment with pegylated interferon-alpha (PEG-IFN-alpha) and ribavirin was attempted in ten SLK patients and a sustained virological response was achieved in 2 patients. Five patients had to stop treatment due to side effects and three had no response. There were no kidney rejection episodes attributable to the antiviral treatment.

As a bonus the study also offers an important insight into the practice and outcome of SLK in a period of transition from pre-MELD to MELD-based organ allocation. SLK patients with higher pre-transplant MELD scores, have longer hospital stays, more infectious complications and reduced 1-year survival of 73.7% as compared to 91.9% in the LTA group ($p = 0.029$). After one year Kaplan–Meyer curves continue in a more parallel fashion. Of note is the finding that all 5 patients receiving expanded criteria donor (ECD) kidneys in combination with the liver died. The reader has to be cautioned, however, that the study does not allow comparison of the outcome of SLK in the presence or absence of hepatitis C, since no appropriate control group (HCV-negative SLK) was studied.

This is the largest study on SLK and recurrent HCV and is also the largest account of treatment of recurrent HCV in SLK. The main conclusion that can be drawn from this paper is that treatment after SLK is feasible and safe since there was no case of a kidney rejection episode. The median follow-up period was reasonably long with a median of almost three years and did not suggest clear differences in the natural history of hepatitis C after SLK as compared to LTA. The treatment outcome cannot be compared due to important differences in genotype distribution.

Limitations of the study include its retrospective design, the lack of uniform indications for SLK (20 out of 38 patients had hepato-renal syndrome before transplant which today would not be considered to be

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Abbreviations: SLK, simultaneous liver–kidney transplantation; HCV, hepatitis C virus; PEG-IFN-alpha, pegylated interferon-alpha; LTA, liver transplantation alone; ECD, expanded criteria donor.

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a good indication for SLK in many patients) and the choice of LTA patients as a control group which were less sick before transplant (their median MELD score was 17.4 versus 38 in the SLK group). The inclusion of a control group consisting of LTA patients matched for their MELD score would have been of interest. The real frequency of recurrent hepatitis C may have been underestimated in the SLK group since fewer liver biopsies were performed, possibly due to reluctance to treat recurrent hepatitis because of the risk of kidney rejection.

In renal transplantation the use of interferon-based treatments is usually discouraged due to the frequent observation of acute rejection seen in older [2] and more recent studies [3] and estimated to be in the 17–100 percent range.

Treatment of recurrent hepatitis C with PEG-IFN-alpha and ribavirin in SLK has been described in the past by Schmitz et al. reporting on their experience with 6 patients (5 with genotype 1 and one with genotype 4) using PEG-IFN-alpha2b (1 μg/kg/week) and ribavirin (600 mg) for 48 weeks. SVR was achieved in 3/6 (50%) patients. None of the patients developed signs of deteriorating kidney function or rejection. One patient without SVR had HCV-related liver graft failure and died 13 months later. Neutropenia (50%) and anemia (50%) were treated with G-CSF and erythropoietin [4].

Several factors have in the past been implicated to have an effect on the outcome of recurrent hepatitis C in the post-transplant period, most importantly the existence of obesity, diabetes and hyperinsulinemia, rapid taper steroid protocols, the choice of calcineurin inhibitor, antiviral treatment, pre-OLT MELD score and the origin of the organ of living versus deceased donors as well as the intensity of immunosuppression, especially steroid boluses, concomitant CMV infection, age of the donor and steatosis of the graft [5–9].

An increased prevalence of glucose metabolism abnormalities in HCV-infected patients was described several years ago in the non-transplant population [10]. The mechanism involves the interaction of HCV with cellular pathways including the insulin signaling cascade as well as intrahepatic inflammation and oxidative stress via TNF-alpha. Some effects were genotype-dependent and are the topic of active research reviewed recently elsewhere [11].

The Bermuda triangle of graft loss consisting of insulin-resistance, HCV and immunosuppressive drugs is addressed by another recently published study from the Mount Sinai Medical Center by del Pozo et al. reporting on 23 HCV-positive SLK transplants as compared to HCV-negative controls and HCV-positive LTA patients [12]. In that study post-transplant diabetes occurred in 80% of the HCV-positive group as compared to 30% of the HCV-negative group ($p = 0.01$). However, overall patient survival for HCV-positive and negative SLK and HCV-positive OLT groups at 1, 2, and 5 years were not significantly different. The study by Van Wagner et al. does not report post-transplant diabetes and we are left not knowing whether it was not observed or simply not reported.

What can we learn from recent data on recurrent hepatitis C after SLK:

- Recurrent hepatitis C after SLK runs a similar course to hepatitis C after LTA and HCV-positive recipients should not be excluded as recipients for SLK.
- Recurrent hepatitis C needs to be diagnosed and treated with PEG-IFN-alpha and ribavirin, using growth factors if necessary, to save the graft in case of severe recurrence.
- The Northwestern University experience would suggest to exclude ECD kidneys from SLK and to offer them to selected kidney transplant recipients.
- Treatment with PEG-IFN-alpha and ribavirin is possible and should be attempted since it cures a significant fraction of patients without elevated risks for the kidney graft.
- It is tempting to speculate that the combined transplantation of kidney and liver may protect the kidney graft against acute rejection induced by PEG-IFN-alpha treatment.

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